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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/678,957	10/03/2003	Wouter Bernard Veldhuis	2183-6141US	7282

24247 7590 06/07/2005

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EXAMINER	
GALVEZ, JAMES JASON	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 06/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/678,957	VELDHUIS ET AL.	
	Examiner	Art Unit	
	J. Jason Galvez	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 October 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/03, 2/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.6.0.

DETAILED ACTION

Election/Restriction

Applicant has presented claims 1-21, filed 10/03/2003, drawn to a method of treating hypoxia/ischemia by administering IFN type-I. Claims 1-21 are pending. Claims 1-21 are under examination.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Drawings

The drawings are objected to because Fig. 4, 8 and 10 recite "treatbin" of the treatment groups. The heading "treatbin" is either a typographic error or a non-standard heading. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the

appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the examiner does not accept the changes, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of reducing tissue damage, cell death and inflammation and improving blood flow as a result of hypoxia/ischemia by administering IFN-β, does not reasonably provide enablement for methods of reducing or preventing tissue damage, cell death and inflammation and improving blood flow as a result of hypoxia/ischemia by administering all type-I Interferons or functional parts, derivatives and analogues of type-I Interferons . The specification does not enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered when determining if the disclosure satisfies the enablement requirement have been summarized as the 1) quantity of experimentation necessary, 2) amount of direction or guidance presented, 3) presence or absence of working examples, 4) nature of the invention, 5) state of the prior art, 6) relative skill of those in the art, 7) predictability or unpredictability of the art, and 8) breath of claims. *Ex Parte Forman*, (230 USPQ 546 (Bd. Pat. App. & Int. 1986)); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Claims 1-21 are drawn to methods of administering type-I Interferons to treat ischemia related complications. Type-I Interferons encompass a number of molecules (Pestka *et al.*, Immunol Rev. 2004, Vol. 202: pp. 8-32, p. 9: Table 1). However, Applicant has only provided evidence that IFN-β can achieve potential therapeutic outcomes following hypoxia/ischemia. Since there is no evidence or rationale for the broad nature of the claim, *i.e.* using all type-I Interferons to treat hypoxia/ischemia related conditions, a person of ordinary skill in the art would not know how to use the instant invention.

Claims 1-21 are drawn to methods of administering functional parts, derivatives, and/or analogues of type-I interferons. Applicant has defined "functional part" to be a part of type-I interferons responsible for post-ischemic damage reduction activity (p. 16: [0054]). However, what makes up the part of type-I interferons responsible for post-ischemic damage reduction activity is not disclosed in the instant specification and/or known in the art. As such, a person

of ordinary skill in the art would not know how to make the invention as claimed. Regarding derivatives and/or analogues of type-I interferons, Applicant has not further limited what these molecules may encompass. Therefore, the claims read on any derivative and/or analogue of type-I interferons and include short peptides, as few as 4-5, that may be used to generate antibodies directed to type-I interferons. Because the claims read on functions and properties other than the function of interest, a person of ordinary skill in the art would not know how to use the invention as claimed. For example, would a stretch of amino acids used to generate antibodies to type-I interferons operate properly in the instant method, *i.e.* would a short peptide used to generate antibodies confer any therapeutic value against complications associated with hypoxia/ischemia?

Furthermore, it is well known in the art that protein structure/function activities are highly dependent on primary structure and that alterations in primary structure can affect the activity of the protein of interest. For example, Luck *et al.* have reported that even conservative, single amino acid changes can measurably alter polypeptide activity (Molecular Endocrinology 1991, Vol. 5(12): pp. 1880-1886, esp. p. 1881, table 1). Additionally, nature has demonstrated that single nucleotide changes can cause altered protein function and phenotypic changes resulting in disease, *e.g.* sickle cell anemia (Stuart *et al.*, Lancet. 2004, Vol. 364(9442): pp. 1343-1360, esp. p. 1344: column 1, paragraph 2).

Claims 1-9 read on methods of administering "a dose of IFN type-I". A dose encompasses the administration of sub-therapeutic concentrations of type-I Interferons. As such, the claims read on administering doses encompassing a

single type-I Interferon to treat hypoxia/ischemia related complications. It is reasonable for a skilled artisan to assume, a dose consisting of a single type-I Interferon would have no effect on any outcome resulting from hypoxia/ischemia. Similarly, claims 10-21 read on administering "IFN type-I" without any requirement for doses and encompass identical issues raised for claims reading on administering "a dose of IFN type-I".

Claim 11 is drawn methods of "at least in part preventing cell death". As such, the claim can be interpreted to mean an absolute prevention of cell death because Applicant merely states "at least". The claim reads on preventing cell death to a single cell to preventing cell death to every cell. Applicant has shown that a type-I Interferon, IFN-β, can decrease lesions following hypoxia/ischemia, but do not show evidence of totally preventing cell death, *i.e.* no lesion. It would not be reasonable to expect a total prevention of cell death following hypoxia/ischemia. There is no evidence in the literature of any treatment that can totally prevent cell death following hypoxia/ischemia, nor has Applicant shown this phenomenon. Furthermore, the ability to prevent cell death requires one to have the ability to predict the occurrence of the pathological condition of interest, in this case hypoxia/ischemia, and the ability to unequivocally show complications or results of said pathological condition were prevented. Under experimental conditions this is theoretically possible because hypoxia/ischemia is induced, but in nature the reality of predicting and preventing hypoxia/ischemia and hypoxia/ischemia related complications has not been an established achievable objective.

Claim 12 reads on methods of "treating blood flow recovery in a subject". The claim does indicate any particular etiology associated with impaired blood flow. Therefore, the claim reads on unrelated conditions not supported by the instant specification, such as orthostatic hypotension. Orthostatic hypotension relates to vascular reactivity, which may result in acute blood flow insufficiencies to the brain and syncope. There is not indication that type-I Interferons would have any therapeutic effects for the treatment of orthostatic hypotension.

For the reasons set forth, without further guidance, a person of ordinary skill in the art would not be able to practice the invention commensurate in scope with the claims without undue experimentation.

Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-21 are drawn to a method of administering functional parts, derivatives, and/or analogues of type-I Interferons. The mere recitation a "functional part" defined as part of type-I Interferons responsible for post-ischemic damage reduction activity is not adequate because the part of type-I Interferons responsible for post-ischemic damage reduction activity is not disclosed in the instant specification or known in the art. In addition, derivatives and/or analogues of type-I Interferons were in no way limited by the instant specification. For example, "derivatives can be, for instance obtained by

conservative amino acid substitution", does not adequately limit the genus of molecules encompassed (p. 16: [0055]). The specification does not impart adequate distinguishing identifying characteristics of the claimed genus of molecules encompassed by functional parts, derivatives, and/or analogues of type-I Interferons.

The claims further encompass the broad class of type-I Interferons. Type-I Interferons are a growing and evolving class of molecules. Therefore, the claims are drawn to using molecules that Applicant does not posses and have yet to be discovered and/or classified as type-I Interferons. As such, a person of ordinary skill in the art would not be able to envisage or predict molecules encompassed by the claimed genus of molecules used in the method as claimed.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is a partial structure in the form of a functional part, derivative, and/or analogue of type-I Interferons. There is not even identification of any particular portion of the structure that must be conserved. As stated above, it is not even clear what region of the protein is needed for activity. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states: "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, a person of ordinary skill in the art cannot envision the detailed chemical structure of the encompassed genus of polypeptides to be used in the claimed method, and therefore conception is not achieved until reduction to practice has occurred regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention, the compound(s) itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only methods using IFN-β, the type-I Interferon disclosed in the instant invention, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claims 1-21 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Omitted steps include a measuring step and a correlation step. The method as claimed is incomplete because Applicant has not designated any outcome markers for the instant method or any correlative relationship of any outcome measures. For example, what does Applicant intend to measure to establish improvement of blow flow in post-ischemic tissue? Likewise, how does the target entity measured correlate to some control that would allow an interpretable result?

Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites, "a pharmaceutically acceptable manner". It is unclear what is meant by and what is encompassed by "a pharmaceutically acceptable manner". As such, a person of ordinary skill in the art would not be apprised of the metes and bounds of the method as claimed so know the breadth of patent protection and possible infringement.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wee Yong *et al.* (Neurology 1998, Vol. 51(3): pp. 682-689 **actual pp. 1-15) in view of Boyle *et al.* (Ann Thorac Surg. 1996, Vol. 62(6): pp. 1868-1875) and Saikumar *et al.* (Oncogene 1998, Vol. 17(25): pp. 3341-3349). Wee Yong *et al.* teach IFN-β, a type-I Interferon, is immunosuppressive and possesses various anti-inflammatory properties, *e.g.* inhibits T lymphocyte proliferation, reduces production of proinflammatory cytokines, and decreased cell adhesion to endothelial cells (p. 3-5; p. 8: paragraph 1). However, Wee Yong *et al.* do not teach the use of IFN-β to treat hypoxia/ischemia and/or inflammation for alleviating associated cell damage, cell death and impaired blood flow resistance.

Boyle *et al.* teach hypoxia/ischemia related blood flow resistance is an inflammatory process and anti-adhesion molecule therapy is effective (p. 1872: Fig. 3; p. 1872: column 2 to p. 1873: column 1, paragraph 1; p. 1873: column 2,

paragraph 2). Hypoxia/ischemia related blood flow resistance has been interpreted to encompass a phenomenon termed to "no-reflow" resistance, which is an inability to adequately perfuse previously ischemic tissues. This interpretation has been made in light of the claim language and the specification where Applicant describes the scenario as "...resistance to the increased blood flow following removal of the obstruction...inflammatory like responses are typically observed in these situations" (p. 3: [0004]).

Saikumar *et al.* teach the inflammatory process is reponsible for cell damage and cell death as a result of hypoxia/ischemia (p. 3341: column 2, paragarph 1).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use IFN-β, a type-I Interferon, to treat hypoxia/ischemia related complications including blood flow resistance and cell damage/cell death as a result of hypoxia/ischemia, because hypoxia/ischemia related blood flow resistance, *i.e.* "no-reflow" phenomenon, and cell damage/cell death is an inflammatory process and IFN-β has anti-inflammatory properties. Additionally, a person of ordinary skill in the art would be motivated to combine the teachings of Wee Yong *et al.*, Boyle *et al.*, and Saikumar *et al.* because hypoxia/ischemia related blood flow resistance, *i.e.* "no-reflow" phenomenon, and cell death can occur following successful removal of obstructive materials. Finally, the expectation of success is reasonably assured because the art teaches IFN-β has anti-inflammatory properties and hypoxia/ischemia related

blood flow resistance, including cell death as a result of hypoxia/ischemia, is also known in the art to be an inflammatory process.

It is noted that there is no indication in the art that hypoxia/ischemia is markedly different in various parts of an organism. When blood supply is not adequate to support cellular respiration the cell eventually dies. The brain, spinal cord, heart, transplanted organs or limbs react similarly in response to hypoxia/ischemia. Therefore, IFN-β would be expected to be effective in all recited organs since the consequences of hypoxia/ischemia are the same.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Sano *et al.* (EP 0 797 998 A1; pub. date: 01/1997). Sano *et al.* teach a method of using type-I Interferons, including IFN-β, to treat cardiovascular diseases and/or complications (column 5: lines 28-32; column 6: lines 1-11). Types of cardiovascular diseases and/or complications include: brain and heart infarction, ischemic vascular disorders, blood flow insufficiency, vascular restenosis, and vascular disorders related to inflammatory processes (column 5: lines 33-59). Furthermore, Sano *et al.* teach the method may be used to treat necrosis as a

result of angiitis, which leads to "clot formation" and "aneurysm formation" (column 5: lines 51-59). Thus, Sano *et al.* meet the limitations of the claims.

Claims 1-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Sano E. (JP 09151137; pub. date: 10/1997). Sano E. teaches a method of using IFN-β in the transplantation of organs and to treat various cardiovascular conditions, including restenosis after PTCA, intima hyperplasia after arteriosclerosis, and vasculitis in artery occlusion (see abstract). Furthermore, the method taught by Sano E. would inherently be effective for reducing cell death following hypoxia/ischemia because, for example, a method directed to treating restenosis following PTCA would inherently, whether appreciated or not, decreases cell death as a result of treating restenosis. Thus, Sano E. meets the limitations of the claims.

Double Patenting

Claims 1-21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of copending Application No. 10/676,847. Although the conflicting claims are not identical, they are not patentably distinct from each other because both inventions are directed to a method of treating hypoxia/ischemia using type-I Interferons. The instant invention is directed to a method of treating hypoxia/ischemia using type-I Interferons, whereas the copending application is directed to a method of treating hypoxia/ischemia using IFN-β, which is in the class of type-I Interferons. The copending application does not specifically recite

treating hypoxia/ischemia related inflammation, but inflammation is an inherent consequence of hypoxia/ischemia that is well known in the art (see previously cited references: Boyle *et al.* and Saikumar *et al.*). The claims of the instant invention correspond to the claims from the invention of the copending application in the following manner:

- Claims 1-9, 11 and 15-21 correspond to claim 17 because the claims are both drawn to methods of treating cell damage/death following hypoxia/ischemia using IFN-β, claimed more generically as IFN type-I in the instant application.
- Claims 10 and 12-14 corresponds to claims 1-16 because the claims are both drawn to methods of treating blood flow resistance complications following hypoxia/ischemia using IFN-β, claimed more generically as IFN type-I in the instant application

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

NO CLAIMS ARE ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **J. Jason Galvez, Ph.D**. whose telephone number is **571-272-2935**. The examiner can normally be reached Monday through Friday 9 AM to 5 PM. If attempts to reach the examiner by telephone are

unsuccessful, the examiner's supervisor, **Brenda Brumback, Ph.D.** can be reached at **571-272-0887**.

The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

JJG
6/02/2005

JANET ANDRES
PRIMARY EXAMINER